Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296-304. DOI: 10.1056/NEJMoa1210357

Supplementary Appendix

Supplement to: Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, MD, Steven R. Goldsmith, MD, Kerry L. Lee, PhD, Michael M. Givertz, MD, Christopher M. O'Connor, MD, David A. Bull, MD, Margaret M. Redfield, MD, Anita Deswal, MD, MPH, Jean L. Rouleau, MD, Martin M. LeWinter, MD, Elizabeth O. Ofili, MD, MPH, Lynne W. Stevenson, MD, Marc J. Semigran, MD, G. Michael Felker, MD, Horng H. Chen, MD, Adrian F. Hernandez, MD, Kevin J. Anstrom, PhD, Steven E. McNulty, MS, Eric J. Velazquez, MD, Jenny C. Ibarra, RN, MSN, Alice M. Mascette, MD, Eugene Braunwald, MD

Contents

CARRESS-HF MEMBERS, INVESTIGATORS AND COMMITTEES

The following individuals participated in the CARRESS-HF study: **Heart Failure Network (HFN) Steering Committee Chair**—*Brigham and Women's Hospital,* E. Braunwald. **HFN Executive committee**—*Brigham and Women's Hospital,* E. Braunwald; *Duke Clinical Research Institute,* K. Lee; *NHLBI,* A. Mascette. **HFN Member Clinical Centers**—*Baystate Medical Center:* M. Slawksy, J. Fleurent, J. Hegeman; *Harvard University*: L. Stevenson, M. Semigran, S. Anello, K. Brooks, D. Cocca-Spofford, M. Givertz; *CentraCare; Heart and Vascular Center at Saint Cloud Hospital:* T. Schuchard, J. Humbert; *Duke University Medical Center*: C. O'Connor, M. Felker, P. Adams, K. Rohrback; *Essentia Health Saint Mary's Medical Center:* K. Boddicker, P. Lipinski; *Hennepin County Medical Center*: B. Bart, S. Goldsmith, S. Mackendanz; *Hospital General Juif:* R. Sheppard, N. Lapointe, K. St. Laurent; *Intermountain Medical Center:* A. Kfoury, J. Tuinei; *Mayo Clinic:* M. Redfield, B. Kaping, S. Milbrandt, J. Gatzke; *Mayo Clinic—Phoenix:* E. Steidley, B. Knight, A. Lizzul; *Michael E. DeBakey V.A. Medical Center*: B. Bozkurt, A. Deswal, A. Chee; *Minneapolis V.A. Medical Center:* I. Anand, K. Geyen; *Montreal Heart Institute:* J. Rouleau, A. Ducharme, J. Morrissette, H. Brown; *Morehouse School of Medicine*: E. Ofili, J. Cross; *North Memorial Heart and Vascular Institute*: G. Hanovich, L. Miller; *Saint Lukes Hospital and Health Network:* A. Potash, E. Taff; *The Methodist Hospital:* J. Estep, P. Brinegar; *The University of Vermont—Fletcher Allen Health Care*: M. LeWinter, L. Chadwick, M. Rowen; *Tufts Medical Center*: D. DeNofrio, D. Fleck, J. Scanlon; *University of Connecticut Health Center*: J. Ryan, M. Barry, I. Collins; *University of Texas Medical Branch:* A. Barbagelata, D. Altmus; *University of Utah School of Medicine*: D. Bull, R. Rosenberg, P. Meldrum; *Utah V.A. Medical Center*: J. Stehlik, R. Rosenberg. **HFN Data and Safety Monitoring Board**—D. Vaughan, J. Berg, M. Johnson, J. Johnson, K. Kennedy, B. Greenberg, J. Parillo, M. Penn, E. Rose; **Protocol Review Committee**—W. Abraham, J. Berg, J. Cai, D. McNamara, J. Parillo, E. Rose, D. Vaughan, R. Virmani; **Biomarker Core Lab**—*University of Vermont:* R. Tracy, E. Cornell, R. Boyle. **Data Coordinating Center**—*Duke Clinical Research Institute*: K. Lee, A. Hernandez, K. Anstrom, E. Velazquez, S. McNulty, J. Sharp, J. Ibarra. **NHLBI Representatives**—A. Mascette, P. Desvigne-Nickens, A. Agresti, J. Keleti, G. Sopko, M. Shah, M. Kwak.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria from final protocol:

- age 18 or older
- admitted to the hospital with a primary diagnosis of decompensated heart failure
- onset of cardiorenal syndrome after hospitalization or pre-hospitalization
    - after hospitalization—onset of cardiorenal syndrome after hospitalization must occur within 10 days from the time of admission after receiving IV diuretics
    - pre-hospitalization—onset of cardiorenal syndrome pre-hospitalization must occur within 12 weeks of the index hospitalization in the setting of escalating doses of outpatient diuretics
- persistent volume overload
    - for patients with a pulmonary artery catheter, persistent volume overload will include:
        - pulmonary capillary wedge pressure greater than 22mmHg and one of the following clinical signs:
            - at least 2+ peripheral edema and/or
            - pulmonary edema or pleural effusions on chest x-ray
    - for patients without a pulmonary artery catheter, persistent volume overload will include at least two of the following:
        - at least 2+ peripheral edema
        - jugular venous pressure greater than 10 cm on physical examination (or central venous pressure greater than 10 mmHg when measured)
        - pulmonary edema or pleural effusions on chest x-ray

Exclusion criteria from final protocol:

- intravascular volume depletion based on investigator's clinical assessment
- acute coronary syndrome within 4 weeks
- indication for hemodialysis
- creatinine > 3.5 mg per deciliter at admission to the hospital
- systolic blood pressure < 90 mmHg at the time of enrollment
- alternative explanation for worsening renal function such as obstructive nephropathy,
- contrast induced nephropathy, acute tubular necrosis
- Hematocrit > 45%
    - poor venous access
    - clinical instability likely to require the addition of intravenous vasoactive drugs, vasodilators and/or inotropic agents
    - allergy or contraindications to the use of heparin
    - the use of iodinated radio contrast material in the last 72 hours or anticipated use of IV
    - contrast during the current hospitalization
    - known bilateral renal artery stenosis
    - active myocarditis
    - hypertrophic obstructive cardiomyopathy
    - severe valvular stenosis
    - complex congenital heart disease
- sepsis or ongoing systemic infection
- enrollment in another clinical trial involving medical or device based interventions

STEPPED PHARMACOLOGIC CARE ALGORITHM

- Intravenous diuretics will be used to address signs and symptoms of congestion

- The stepped pharmacologic care 'intervention' will be finished when the patient's volume status has, in the opinion of the investigator, been optimized and there is no ongoing need for intravenous diuretics (patients may require the stepped pharmacologic care 'intervention' beyond the 96 hour primary endpoint assessment)

- A stepped care algorithm developed by the Heart Failure Network is provided below

- Investigators may opt-out of the stepped care treatment algorithm if they feel it is in the best interests of patient care

- Careful clinical monitoring is necessary so that volume reduction therapy can be reduced as patients approach an optimized volume state. Blood pressure, physical exam findings, hemodynamics, BUN and creatinine should be used to determine optimal volume status

- Intravenous diuretics can be decreased or temporarily discontinued if there is a decrease in blood pressure or an increase in creatinine that is felt to be due to a transient episode of intravascular volume depletion. After the patient has stabilized, if congestion persists, intravenous diuretics should be reinitiated until the patient's fluid status has been optimized.

- Crossover to ultrafiltration is discouraged before the 96 hour primary endpoint assessment

- The transition from IV to oral diuretics prior to discharge is left to the discretion of the treating physician and will be continued in the outpatient setting as needed for optimal fluid homeostasis

AT RANDOMIZATION – STEPPED PHARMACOLOGIC CARE ARM

UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → See table

	Current Dose		Suggested Dose	
	loop (/day)	thiazide	loop (/day)	thiazide
A	≤ 80	+ or -	40 mg iv bolus+ 5 mg/hr	0
B	81-160	+ or -	80 mg iv bolus+ 10 mg/hr	5 mg metazolone QD
C	161-240	+ or -	80 mg iv bolus+ 20 mg/hr	5 mg metazolone BID
D	> 240	+ or -	80 mg iv bolus+ 30 mg/hr	5 mg metazolone BID

AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms

AT 72 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (Any EF) and Severe Symptoms
Advanced Cardiorenal Therapy Hemodynamic guided iv therapy, LVAD, Dialysis or UF Cross over

AT 96 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (Any EF) and Severe Symptoms
Advanced Cardiorenal Therapy Hemodynamic guided iv therapy, LVAD, Dialysis or UF Cross over

CARRESS-HF END POINTS

Primary End Point

Change in serum creatinine AND weight together as a "bivariate" endpoint assessed 96 hours after enrollment.

Secondary End Points

a) Primary endpoint (change in serum creatinine AND weight together as a "bivariate" endpoint) assessed after randomization on hospital days 1 - 3 and at one week.

b) Significant weight loss and renal improvement assessed at 96 hours and one week.

c) Treatment failure during the first seven days after randomization.

d) Changes in renal function from randomization to days 7, 30 and 60. Peak creatinine during hospitalization.

e) Changes in electrolytes from randomization to 96 hours and one week.

f) Changes in weight measured daily from randomization to one week, 30 and 60 days.

g) Percent of patients achieving clinical decongestion at 96 hours, one week, 30 and 60 days.

h) Total net fluid loss from randomization to 96 hours and 1 week.

i) Changes in biomarkers from randomization to 96 hours, at one week and at 60 days.

j) Changes in global assessment and visual analogue scores from enrollment to 96 hours and one week.

k) Length of hospital stay from time of enrollment to discharge, days alive outside the hospital at 60 days, and heart failure rehospitalizations during the 60 day followup, unscheduled emergency department and office visits.

l) Changes in daily oral diuretic doses from prior to hospitalization to discharge, at 30 and at 60 days.

m) Resource utilization as described in item K above plus the number of disposables consumed by the ultrafiltration intervention

FIGURE S1: CONSORT FLOW DIAGRAM

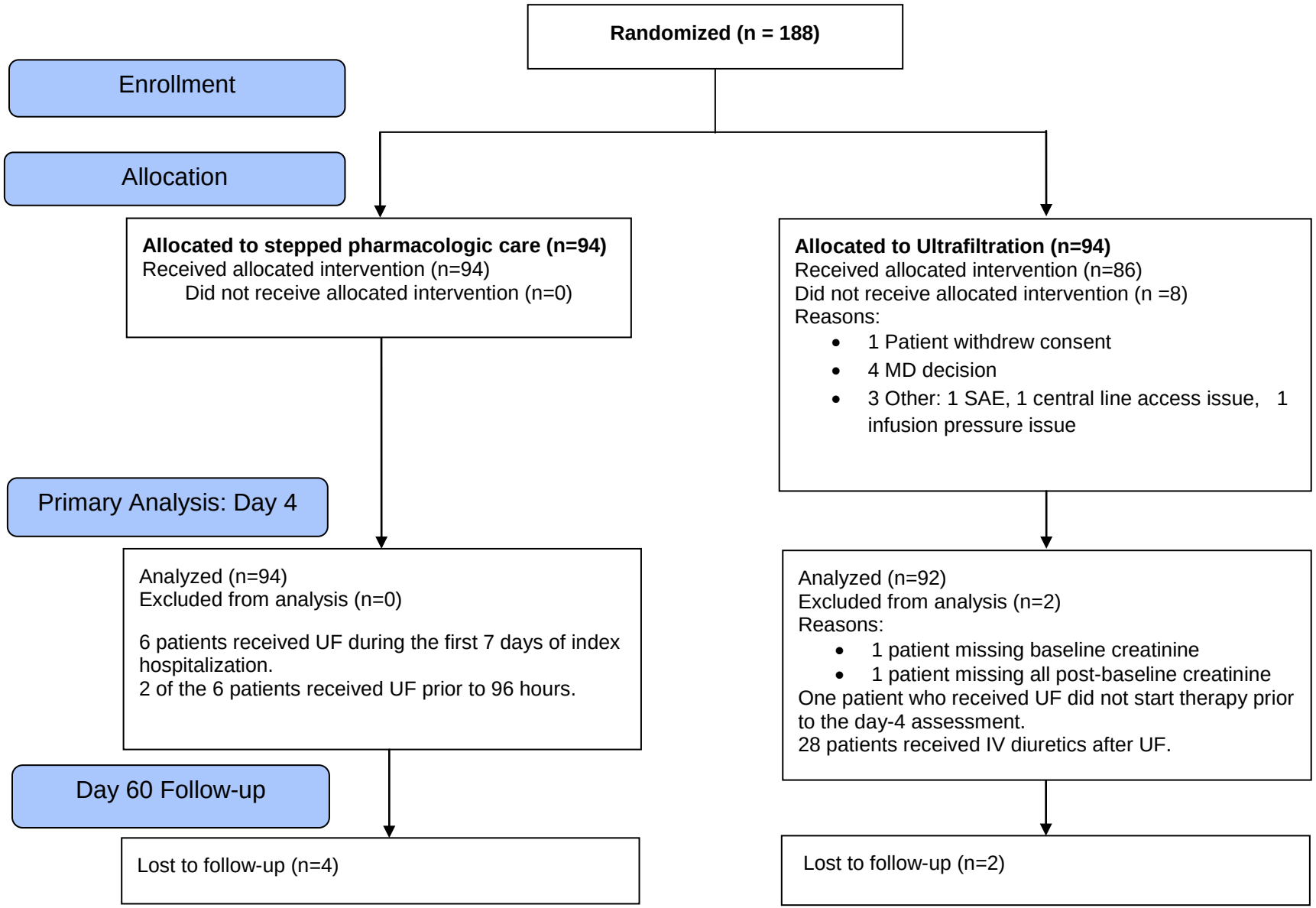


FIGURE S2: 95% CONFIDENCE REGION (ELLIPSE) FOR THE MEAN TREATMENT DIFFERENCES AT 96 HOURS

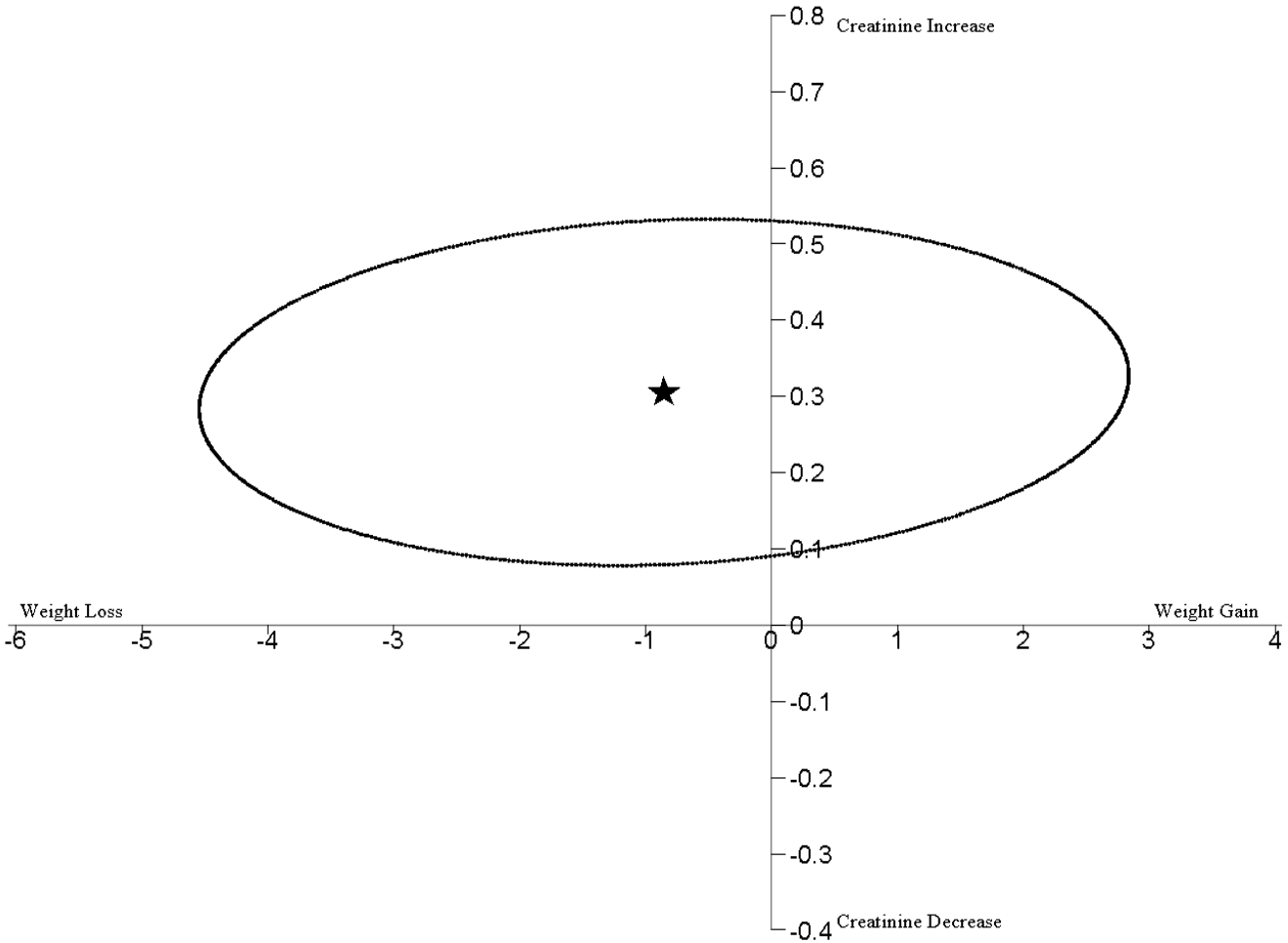
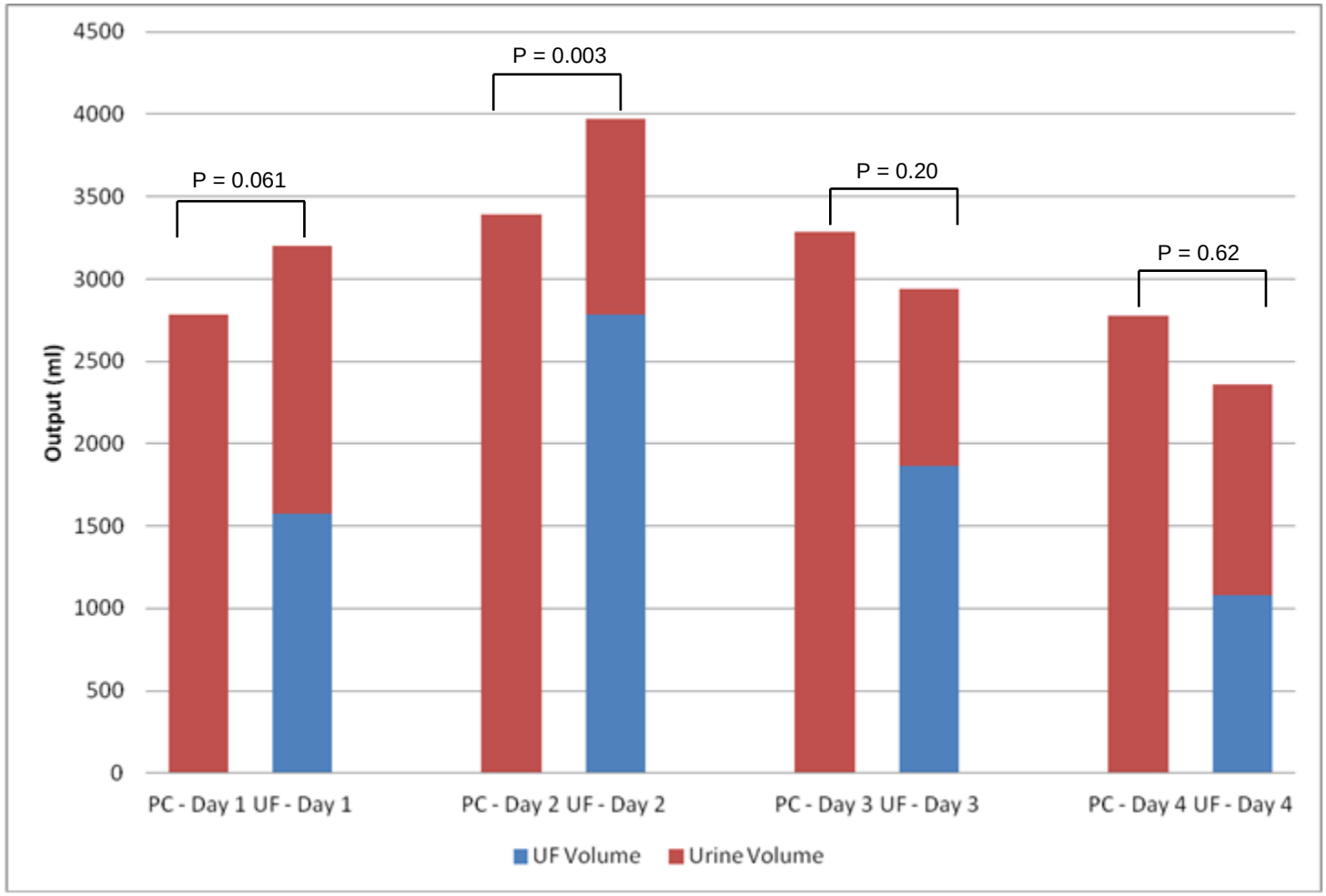
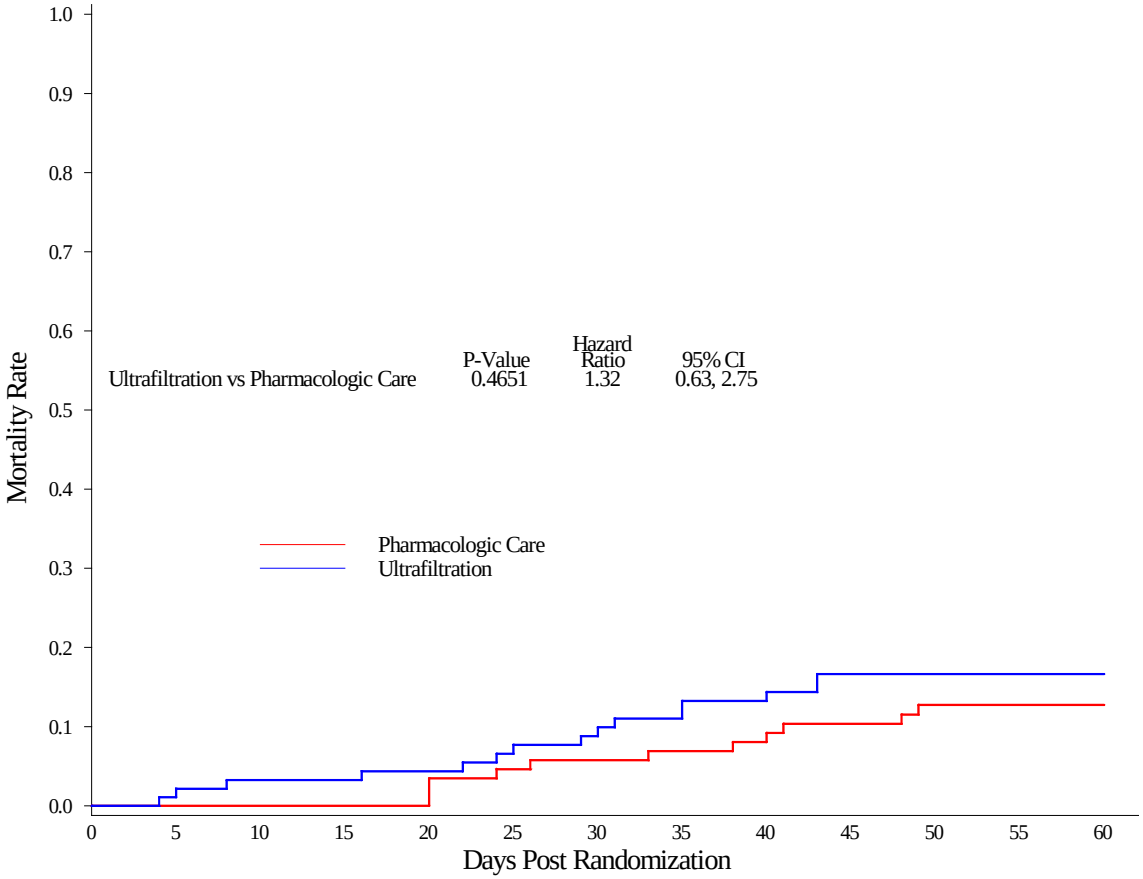


FIGURE S3: TOTAL FLUID OUTPUT BY DAY



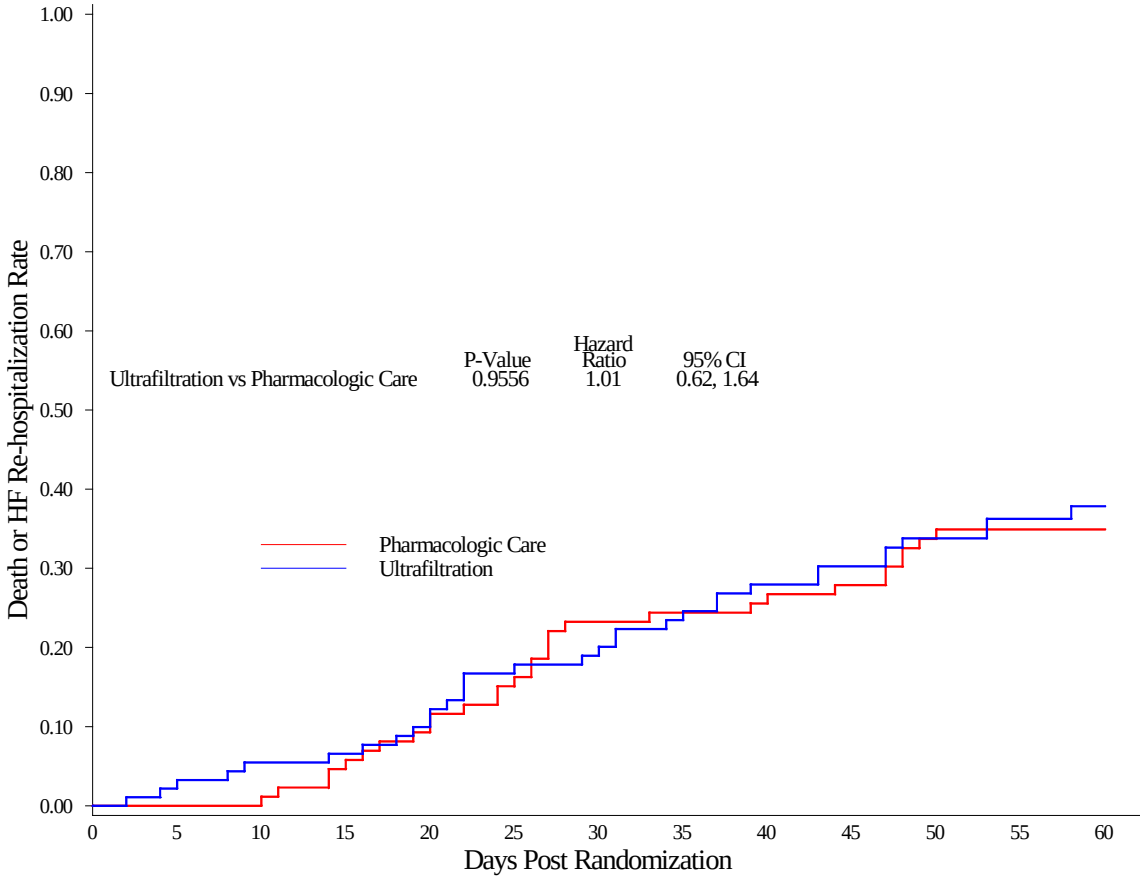
PC=Pharmacologic care; UF=Ultrafiltration

FIGURES S4: KAPLAN-MEIER TIME TO DEATH



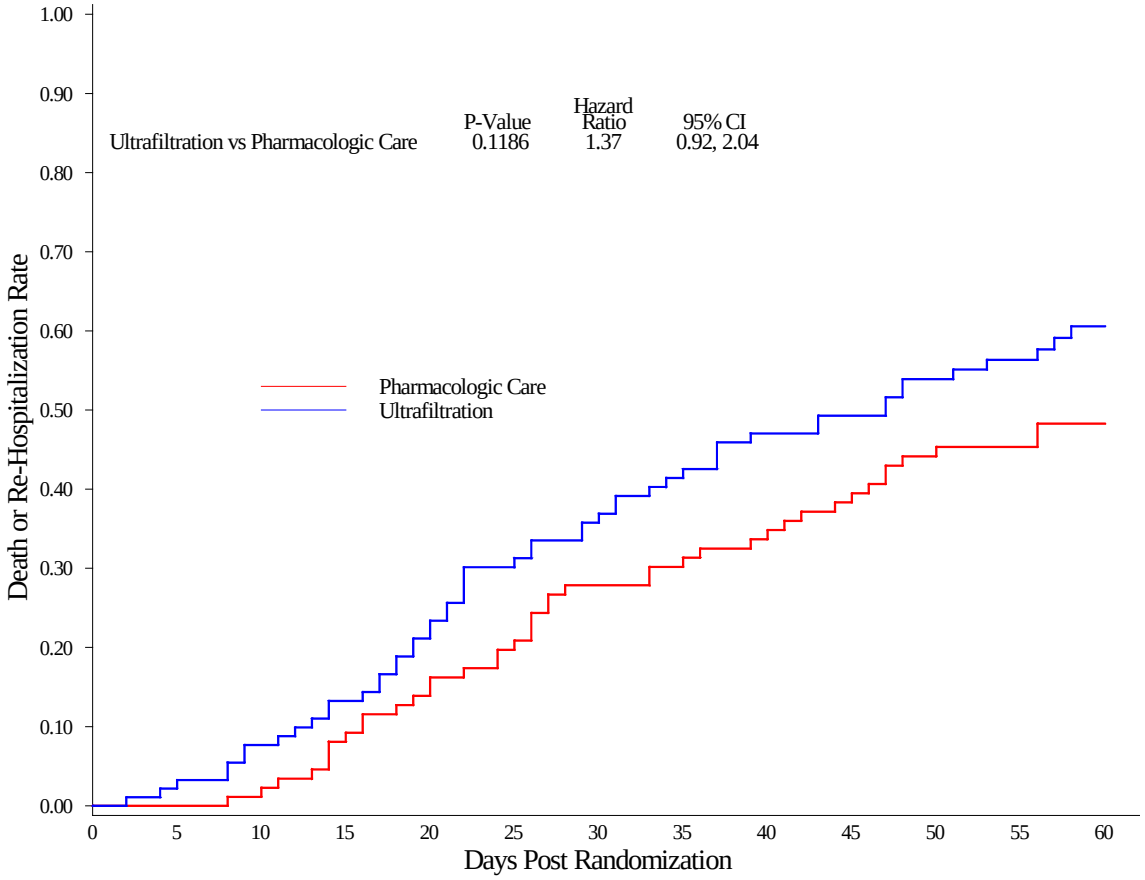
Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	94	92	88	87	87	83	82	81	80	77	72	61	40
Ultrafiltration	94	92	88	88	86	84	82	80	78	73	70	64	44

FIGURE S5: KAPLAN-MEIER TIME TO DEATH OR HEART FAILURE REHOSPITALIZATION



Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	93	91	87	82	78	73	66	65	64	62	56	47	32
Ultrafiltration	93	90	85	84	80	74	72	68	64	61	55	51	36

FIGURE S6: KAPLAN-MEIER TIME TO DEATH OR ANY REHOSPITALIZATION



Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	93	91	86	79	74	69	62	60	57	53	47	40	25
Ultrafiltration	93	90	83	78	70	62	57	52	47	45	39	36	24